claims 1 and 7, and have further amended those claims. Applicants have also amended claims 3 and 9 in response to the rejections in the October 12 Office Action. All claims stand rejected. Applicants respectfully traverse the rejections for the reasons set forth below.

Preliminary Statement

The inventions disclosed and claimed in this application represent breakthrough technology. These inventions provide for the first time genetically engineered monoclonal antibodies that when topically applied provide a mammal with a humoral immune response to antigens to which the antigens to which the mammal may had a different or more limited response. To applicants' knowledge, this has not previously been possible. In this application, the antigen is present on the surface of the bacteria believed to cause tooth decay, *Stretococcus mutans*. Mammals respond to this bacterial infection by secreting antibodies of the IgA serotype -- a secretory antibody. Secretory antibodies do not kill the infecting bacteria.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 5, 11 and 13-16 stand rejected as not enabled for embodiments of the invention in which *Brassica napus*, or edible plant other than *Arabidopsis thaliana* are used for production of chimeric antibodies. Applicants are concerned that the Examiner may have misapprehended Applicants' response to the prior rejections under § 112, first paragraph.

To begin with, *Brassica* is a genus of edible plants that includes turnip, kale, cauliflower cabbage, broccoli and other forage crops. *See* Specification at 13. As also stated in Applicants' specification *Arabidopsis thaliana* is closely related to *Brassica*. Indeed, as established by the

web pages attached hereto as exhibits, *Arabidopsis* is used as a model system for *Brassica*. "We chiefly study the various *Brassic* crop species that have a close taxonomic relationshiip with the model species *Arabidopsis thaliana* ." (www.jic.bbsrc.ac.uk/science/brassica); "The sequence tools that we have developed for the*Arabidopsis* cDNA sequencing project have been adapted for use with *Brassica napuus*." (www.cbc.umn.edu/Research/Projects/Brassica/index.html) Because the reproductive cycle for *Arabidopsis* is shorter than that of Brassica, Arabidopsis is frequently used for laboratory experiments. That is, it is a "model system" that is convenient for scientific investigations:

> A useful model plant to carry out mutagenesis screens is *Arabidopsis thaliana*. It is naturally self fertilizing, produces abundant weed within 6-8 wk after gernamination and grows vigoursoely in artificial light and in vitro. It has recently received a larte amount of attention for molecular biological studies..

J. Topping et al., Agrobacterium-Mediated Transformation of *Arabidopsis thaliana*. (submitted with Response mailed October 12, 2000.). Hence the relevance of results obtained in studies of *Arabidopsis* to other plants is a matter generally accepted by plant scientists.

The text quoted by the Examiner from page 79 of the Thomzik document, from which the Examiner concludes that "it is extremely remote that said protocols would be effective in other species" (Office Action at page 4) is Thomzik's summary of the background to the investigations reported in his paper. With respect to his studies, Thomzik states "slight modification of the transformation protocol used for cv. Westar (l) led to a simple transformation system, which also works with high efficiency for winter oilseed rape" (i.e., *Brassica*). The transformation protocol,

set forth at pages 80-82 thereof, uses the same vector for transformation as is used in studies with Arabidopsis, *Agrobacterium tumorfaciens*..

The Ma document, (European J. Immunol. 1994:131-138), relied on by the Examiner, also views the results of cloning experiments with plants as properly generalized:

> Furthermore, mAb generated in plants might be more acceptable as topical therapeutic agents. mAb-producing plants can be derived from a sexual cross between plants individually expressing mAb heavy and light chains; the assembly of immunoglobulin chains is extremely efficient.

Although Ma used tobacco plants to express immunoglobulin, his discussion in this and other publications previously cited refers to "plants."

Rejections For Lack Of Novelty

Claims 1, 6 and 7 stand rejected as anticipated under 35 U.S.C. § 102(b) by Lehner, United States patent 5,352,446. According to the Examiner, Lehner discloses the oral administration of murine monoclonal antibodies to *S. mutans* for the treatment and prevention of dental caries in man. Applicants have obviated this rejection by amending the independent claims to make explicit that the monoclonal antibodies of the present invention are chimeric.

Rejections For Obviousness

Claims 1-4, 6-10, 12 and 17 stand rejected under 35 U.S.C. § 103(a) in view of Ma, Europeam J. of Immunology, and Adair et al., United States patent 5,877,293. According to the Examiner, Ma differs from the claimed invention in that both the heavy and light chains of the

chimeric monoclonal antibodies are derived from mouse, while Adair discloses methods for production of chimeric antibodies where the light chains are murine and hearvy chains are human antibodies. The Examiner contends that it would be obvious to "humanize" the chimeric monoclonal antibodies disclosed in the methods of Ma with the human heavy chain regions of Adair et al.

Applicants respectfully traverse this rejection for the reasons set forth in their Response dated October 12, 2000 and for the additional reasons set forth below. Even if the teachings of the two documents were combined, the result would not teach or suggest applicants' claimed invention. Applicants submit that the rejection for obviousness is based on hindsight reconstruction of their claims and a very limited reading of the Ma document.

Ma refers to the expression of genetically engineered immunoglobulin constructs *S. mutans* bacteria believed to cause tooth decay (dental caries). The constructs are secretory antibodies -- not humoral antibodies -- that were specifically designed to prevent caries by blocking a protein secreted by *S.,mutans* and believed necessary for the bacteria to adhere to tooth surfaces. *See* Ma at p. 131.

With regard to arguments already of record, applicants respectfully disagree that the combination of the references cited by the Examiner teach or suggest:

> A method for the treatment and prevention of dental caries in a mammal comprising oral administration of a chimeric monoclonal antibody that specifically binds to at least one cariogenic organism, and <u>which elicits a humoral immune response to antigens displayed by cariogenic organisms from the mammal</u>.

In the pending Office Action the Examiner states:

> Applicant is reminded that the aforementioned rejection is based on the combination of the cited references (see above) and not independently. Said combination clearly encompasses all the limitations of the claimed invention. Additionally, as pointed out by Applicant, the construction of chimeric and humanized antibodies and the tailoring of the constant regions (i.e., selection of isotypes specific for cell mediated cytotoxicity) is well known in the art. see Kipriyanov et al., Molecular Biology, Vol. 12, pages 173-201).

The Examiner's remarks do not explain how the limitation that the claimed method of treatment results in the ability of the treated mammal to mount a humoral response to a cariogenic organism. Indeed, the Examiner never refers to the limitation, though the issue was specifically raised in applicants' response dated October 12, 2000:

> Applicants' invention includes a method for treatment of dental caries wherein a chimeric antibody is capable of both specifically recognizing cariogenic organisms, and eliciting an effector response *to such organisms from the host immune system*. Neither Ma nor Adair, nor any combination of the references teach or suggest this capability.
>
> Unless the constant region of a chimeric monoclonal antibody is capable of activating the host immune system, the binding of antigen to a target organism could at most provide a method for its detection or the delivery of a drug or toxin to the site recognized. No teaching of which applicants are aware suggests the use of chimeric antibodies to bring the effector apparatus of the human immune system to bear on an infectious or otherwise pathological site in the body.
>
> As the cited references do not teach or suggest the claimed invention, the rejection for obviousness should be withdrawn.

(emphasis in original).

In the January 26 Office Action the Examiner relies on Adair to show that it was within the level of skill in the art to humanize the chimeric monoclonal antibodies of Ma. Office Action

at 7. Adair defines the term "humanizing" as "a molecule having an antigen binding site derived from an immunoglobulin from a non-human species, the remaining immunoglobulin derived parts of the molecule being derived from a human immunoglobulin." Combining Adair with Ma would at most suggest a chimeric monoclonal antibody that binds *S. mutans*. The Examiner also relies on a fragment of a sentence in Ma: "However, for other antibodies, there might be significant regions. [sic] such as the complement binding domain from a human IgG1 antibody, or domains from containing regions that act as receptors for cell- or tissue-specific molecules." Ma at p. 137. The Examiner then cites Adair for the proposition that chimeric monoclonal antibodies are less antigenic to humans than mouse antibodies, concluding that one would have a high expectation of success in making the required monoclonal antibodies and using them to treat dental caries.

To the extent that the Examiner relies on the fragmentary and speculative remark in Ma referring to a complement binding protein as suggesting that the passage meets the limitation that the chimeric monoclonal antibody "elicits a humoral immune response to antigens displayed by cariogenic organisms from the mammal" such reliance is factually incorrect.

> The complexing of antibody with antigen induces conformational changes in the Fc portion of the antibody molecule that exposes a binding site for the C1 component of the complement system. C1 exists in serum as a macromolecular complex consisting of C1q and two molecules each of C1r and C1s held together is a comples ($C1qr_2 s_2$) stabilized by calcium ions. The C1q molecuole is composed of 18 polypeptide chains that associate to form six collagen-like triple helical arms, the tips of which bind to exposed C1q binding sites in the C_h2 domain of the antibody molecule.

Janet Kuby, Immunology, Third Edition 1997 at p. 337 (copy provided). While it is unclear what was intended by the fragmentary statement from the Ma document, as shown by the quoted

text from the Kuby text, the statement cannot be viewed as providing a teaching of a method for enabling a mammal to mount a humoral immune response as a complement binding domain would not provide the necessary functionality. The rejection is plainly based on impermissible hindsight reconstruction of the invention.

Moreover, the combination of Ma and Adair does not teach or suggest applicants' invention for the additional reason that the teachings of the cited documents are inconsistent with one another. As previously shown, Adair defines "humanized" monoclonal antibodies as murine antibodies in which all but the immunoglobulin binding site is replaced with human sequences. Ma, on the other hand refers to genetically engineered immunoglobulin molecules that are entirely murine. Office Action at 6. Ma's speculation that there "might" be advantages in "incorporating other functional regions" provides no guidance with regard to the location of such regions, or their relation to the non-functional human sequences referred to by Adair.

In this regard it is important to bear in mind the appropriate perspective for the assessment of obviousness:

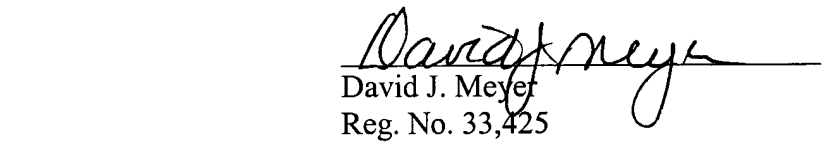
> Obviousness is tested by what the combined teachings of the references would have suggested thoug those ordinarily skilled in the art." But it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. And teachings of references may be combined *only* if there is some suggestion or incentive to do so. ... One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fine*, 837 F.2d. 1071, 1075 (Fed. Cir. 1988) (emphasis in original).

Applicants respectfully submit that the rejections of their claims as obviousness is based on hindsight reconstruction and should be withdrawn.

CONCLUSION

Applicants respectfully suggest that their claims are in condition for allowance, and request issuance of a notice thereof. The Assistant Commissioner is hereby authorized to charge any required fees to Deposit Account No. 131 241, for the pendency of this application and for all fees that may be charged to a deposit account, or to credit any overpayment thereto.

Respectfully submitted
MANATT, PHELPS & PHILLIPS LLP



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